Cardiovascular Morbidity and Mortality Related to Non-alcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis

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Abstract: Whether non-alcoholic fatty liver disease (NAFLD) is a cardiovascular (CV) risk factor is debated. We performed a systematic review and meta-

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; CV, cardiovascular; IQR, interquartile range; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; QUIPS, quality in Prognostic Studies

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analysis to assess the CV morbidity and mortality related to NAFLD in the general population, and to determine whether CV risk is comparable between lean and non-lean NAFLD phenotypes. We searched multiple databases, including PubMed, Embase, and the Cochrane Library, for observational studies published through 2022 that reported the risk of CV events and mortality. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for all-cause mortality, CV mortality, myocardial infarction (MI), stroke, atrial fibrillation (AF), and major adverse cardiovascular and cerebrovascular events (MACCE) were assessed through random-effect meta-analysis. We identified 33 studies and a total study population of 10,592,851 individuals (mean age 53±8; male sex 50%; NAFLD 2, 9%). Mean follow-up was 10±6 years. Pooled ORs for all-cause and CV mortality were respectively 1.14 (95% CI, 0.78-1.67) and 1.13 (95% CI, 0.57-2.23), indicating no significant association between NAFLD and mortality. NAFLD was associated with increased risk of MI (OR 1.6; 95% CI, 1.5-1.7), stroke (OR: 1.6; 95% CI, 1.2-2.1), atrial fibrillation (OR: 1.7; 95% CI, 1.2-2.3), and MACCE (OR: 2.3; 95% CI, 1.3-4.2). Compared with non-lean NAFLD, lean NAFLD was associated with increased CV mortality (OR: 1.50; 95% CI, 1.1-2.0), but similar all-cause mortality and risk of MACCE. While NAFLD may not be a risk factor for total and CV mortality, it is associated with excess risk of non-fatal CV events. Lean and non-lean NAFLD phenotypes exhibit distinct prognostic profiles and should receive equitable clinical care. (Curr Probl Cardiol 2023;48:101643.)

Introduction

Non-alcoholic fatty liver disease (NAFLD) is an emerging health issue with a global estimated prevalence of 25%.[1] While it is debated about whether NAFLD should be considered a cardiovascular (CV) risk factor,[2-5] major international guidelines have recently recognized the need for CV assessment in affected patients.[6] NAFLD is associated with various comorbidities, including dyslipidemia, metabolic

syndrome and diabetes, but the impact of NAFLD on CV morbidity and mortality has not been fully established and remains controversial. There is also accumulating evidence that lean NAFLD population – that may easily escape CV prevention programs – would experience higher rates of CV events. In this systematic review and meta-analysis of observational studies, we aimed to evaluate the relationship between NAFLD and CV morbidity and mortality, and to evaluate whether lean and non-lean NAFLD are different phenotypes with distinct prognostic profiles.

Methods

The current meta-analysis was planned, conducted, and reported in accordance with currently available statements for design, analysis, and reporting of meta-analyses of randomized and observational studies.[7,8] A protocol for the systematic review and meta-analysis was pre-registered at Open Science Framework.[9]

Search Methods for the Identification of Studies

Medline and Embase databases, the Clinical Trials Registry (www.clinicaltrials.gov), as well as abstracts from major cardiological societies meetings were searched for potentially relevant articles using the search terms "NAFLD" or "non-alcoholic fatty liver disease" or "non-alcoholic fatty liver disease" or "NASH" or "nonalcoholic steatohepatitis" or "liver fat" and "cardiovascular mortality" or "cardiovascular death" or "myocardial infarction" or "stroke" or "heart failure" or "atrial fibrillation." We also searched reference lists of all identified articles for additional relevant studies, including hand-searching reviews, and previous meta-analyses. Three authors (G.B., A.S., and E.M.) independently performed the screening of titles and abstracts, reviewed full-text articles, and determined their eligibility. The search was performed for the period from January 1966 to March 2022 and was restricted to the English-language literature. Reviewers were not blinded to study authors or outcomes. Divergences were resolved by consensus and/or by involving another reviewer. Studies reporting on cohorts enrolling NAFLD patients were included in the systematic review if they met the following criteria: (1) published as full-length article, (2) English language, (3) longitudinal study design, (4) minimum follow-up period of 6 months, (5) enrolling adult individuals ($\geq$18 years), and (6) reporting raw data concerning all-cause death, cardiovascular death, myocardial infarction, stroke, heart failure, or atrial fibrillation counts for individuals with and without

NAFLD, and/or in patients with lean NAFLD versus non-lean NAFLD. Study-level lean definition (ie BMI <25 kg/m^2 or <23 kg/m^2) was noted and accepted as reported. Cohorts comparing NAFLD patients versus non-NAFLD subjects were included if they had a prospective study design. Cohorts comparing lean and non-lean NAFLD patients were included regardless of prospective/retrospective study design. If more than one study was identified that reported clinical outcomes for a single specific cohort, the study with the higher number of patient-years was selected for inclusion.

Coding, Data Collection, and Quality Assessment

Three investigators (G.B., A.S., and E.M.) independently abstracted raw data relative to baseline characteristics of studies, patient populations, and outcomes ascertained from original eligible sources, and collected them in a predefined data extraction matrix. Definitions of NAFLD and lean/non-lean status were noted and accepted as reported. The endpoints of interest in the overall analysis were ascertained based on the International Classification of Diseases 9th, 10th, and 11th Revisions (ICD-9, ICD-10, and ICD-11); the ascertainment of events was accepted as reported. Clinical details on patients and study design were abstracted, and internal validity of included observational studies was appraised by means of the QUIPS tool.

Statistical Analysis

Categorical variables were reported as percentages, and continuous variables as means and standard deviation or medians and interquartile range (IQR) as appropriate. Data derived from each study were used to calculate the odds ratio (OR) using the Mantel−Haenszel method for each study outcome. Average effects for the outcomes and 95% confidence interval (CI) were obtained using a random-effects model. Average effects were not calculated for outcomes reported by less than 3 studies. Heterogeneity of the effect across studies was assessed by means of Cochrane Q chi^2 statistics and I^2 statistics. Lack of homogeneity was considered for Cochrane Q chi^2 test P-value ≤ 0.10 and/or for I^2 statistics $\geq 50\%$. The Hartung-Knapp adjustment[10] for random-effects model was applied to all outcome analyses except for those with less than 5 studies per group and for sensitivity analyses, and conventional results without the adjustment were reported in Figure S3.[11,12] The z-statistic was computed for each clinical outcome, and results were considered statistically

significant at a P-value <0.05. Meta-analysis results were presented in forest plots with point estimates of the effect size and 95% CIs for each study as well as for pooled result, with area of each study square proportional to its weight. A Jackknife leave-one-out sensitivity analysis was performed to evaluate the robustness of the results and the impact of each single study on the summary estimate of effect; forest plots for sensitivity analyses are included in Figure S4. The likelihood of publication bias was assessed using funnel plots by displaying individual study OR with 95% CIs for the endpoints of interest, with the addition of nonparametric "trim-and-fill" procedure to adjust for funnel plot asymmetry by generation of hypothetical missing studies; for models including more than 10 studies, funnel plot asymmetry was also evaluated by using the Egger regression asymmetry test ($P < 0.10$ considered as indicative of statistically significant asymmetry). To investigate possible sources of heterogeneity among studies, post hoc subgroup analyses were. Subgroup analysis by geographic location was carried out by dividing patient cohorts based on country where the study took place. Criteria for allocation of studies to Western or Eastern group is detailed in the Supplementary Methods, paragraph 1. All statistical analyses were performed using R (version 4.1.0; packages utilized as in the Supplementary Methods, paragraph 2).

Results

Of 3588 citations identified and retrieved, we identified 224 potentially relevant articles. Of these, 202 publications did not fit our inclusion criteria (outcome data not reported, absence of control group, duplicate study, clinical population other than NAFLD, inadequate study design, clinical population other than NAFLD, unclear/absent definition of NAFLD diagnosis, and incomplete dataset), and were therefore discarded (Fig. S1). We finally included 33 cohort studies, published between 2007 and 2022 and from 12 different countries (7 studies from the United States, 4 from Italy, 3 from South Korea, 5 from Japan, 2 from Sweden, 2 from Finland, 2 from Hong Kong and one each from China, Turkey, Sri Lanka and Egypt; 2 studies comprised cohorts from more than one country (Italy, Spain, the Netherlands, and the United Kingdom in the publication by Alexander and colleagues[13]; Italy, United Kingdom, Spain and Australia from Younes and colleagues[13]), for a total pooled population of 10,592,851 individuals. Average prevalence of NAFLD was 3%, with large inter-study variability (Table 1). Follow-up time ranged from 1.6 to 25 years (median 6.9 years, IQR: 4.9-10.9). Diagnostic modalities for assessing NAFLD status were ultrasonography (16 studies), liver biopsy

TABLE 1. Detail of included studies

Year	First Author	Country	Sample size, n	NAFLD population (%)	NAFLD population (n)	Follow-up, years (median)	Study design	Mean age (y)	Male sex (%)	Type 2 diabetes mellitus (%)	Hypertension (%)	Smokers (%)	NAFLD diagnosis
2022	**Younes et al.**	Italy, UK, Spain, Australia	1339	100	1339	7.8	Retrospective study	48	65	28			Biopsy
2021	**Niriella**	Sri Lanka	2985	32	955	7	Prospective study	52	53	19	37		US
2021	**Ahmed**	United States	4834	100	4834	6.4	Retrospective study	52	46	35	41		ICD
2021	**Ould Setti**	Finland	1552	55	854	3.48	Prospective study	54	100		28	35	FLI
2021	**Pastori**	Italy	1735	42	729	1.6	Prospective study	75	56	24	88	9	FLI
2021	**Meyersohn**	United States	3756	74	2779	25	Prospective study	61	48	20	64		CT
2021	**Ichikawa**	Japan	529	27	143	4.4	Prospective study	65	61	1	71	24	CT
2021	**Feldman**	Austria	296	100	296	8.4	Retrospective study	49,5	72	21	55		Biopsy
2020	**Alvarez**	United States	12249	39	4777	23	Prospective study	39	44	15	31	25	US
2020	**Xu**	China	79905	31	24771	10.34	Prospective study	51	31				US
2020	**Niriella**	Sri Lanka	2724	31	844	10	Prospective study	52	30	23	61		US
2020	**Zou**	United States	14365	33	4740	6.4	Retrospective study		47				ICD
2020	**Yang**	South Korea	7964	15	1195	12	Prospective study	55	35	9	39	21	FLI
2020	**Roh**	South Korea	334280	25	83570	5.3	Prospective study	42	48				FLI
2020	**Hirose**	Japan	223	100	223	19.5	Retrospective study	43,2	66	22	25	36	Biopsy
2020	**Iritani**	Japan	446	100	446	4.6	Retrospective study	52	60	33	45	22	Biopsy
2019	**Baratta**	Italy	898	72	647	3.5	Prospective study	56	62	25	70	23	US
2019	**Hagström**	Sweden	6872	9	618	18.6	Prospective study	48	63				Biopsy
2019	**Alexander**	European Union	9768439	1	85520	5	Prospective study	54	50				ICD
2018	**Hwang**	South Korea	318224	26	82738	5.7	Prospective study	39	52	4	15	23	US
2018	**Allen**	United States	19078	20	3816	7	Prospective study	53	48	15	32		ICD
2018	**Hagström**	Sweden	646	100	646	19.9	Retrospective study	48,2	62	14	30	21	Biopsy
2017	**Yoshitaka**	Japan	1647	19	313	6.8	Prospective study	48	57			25	US
2017	**Long**	United States	2122	20	424	12	Prospective study	59	47	7	26	10	US

(*continued on next page*)

TABLE 1. (*continued*)

Year	First Author	Country	Sample size, n	NAFLD population (%)	NAFLD population (n)	Follow-up, years (median)	Study design	Mean age (y)	Male sex (%)	Type 2 diabetes mellitus (%)	Hypertension (%)	Smokers (%)	NAFLD diagnosis
2017	**Keskin**	Turkey	360	53	191	2.6	Prospective study	59	67				US
2017	**Leung**	Hong Kong	307	100	307	4.1	Prospective study	51	56	55	55		Biopsy
2016	**Fracanzani**	Italy	375	33	124	10	Prospective study	52	87				US
2016	**Wong**	Hong Kong	612	58	355	6	Prospective study	63	71	31	66	32	US
2015	**Käräjämäki**	Finland	958	25	240	16.3	Prospective study	51	47	10	51	15	US
2013	**Targher**	Italy	400	70	280	10	Prospective study	64	59				US
2013	**El Azeem**	Egypt	747	36	269	3	Prospective study	51	49	58	32	22	US
2010	**Adams**	United States	337	34	115	10.5	Prospective study	58	49	1	63	19	US, CT, MR, or liver biopsy
2007	**Hamaguchi**	Japan	1647	19	313	5	Prospective study	48	60				US

(6 studies), fatty liver index (4 studies), ICD coding (4 studies), and computed tomography (2 studies). For comparison between NAFLD patients and non-NAFLD controls, a total of 23 prospective studies were eligible. For the comparison between lean and non-lean NAFLD patients, a total of 10 studies were included, of which 7 were retrospective and three were prospective studies.

The overall quality of included studies was high according to the QUIPS tool (Fig S2). The main characteristics of the included studies are summarized in Table 1.

NAFLD and Mortality

All-cause Mortality. Data on the relationship of NAFLD with all-cause death were reported in 9 studies,[14-22] pooling a total population of 358,095 (NAFLD 26.37%) followed-up for a median of 24.1 years (IQR 5-12, 2,890,614 patient-years). Patients with NAFLD showed a trend toward increased risk of all-cause death when compared to controls, however, this finding did not reach statistical significance (OR, 1.14; 95% CI, 0.78-1.67; $P = 0.459$). The random-effects model showed considerable heterogeneity, with an I^2 of 86%. Funnel plot asymmetry was not assessed by Egger's test due to low number of studies ($n < 10$) (Figure 1).

Cardiovascular Mortality. Data on the relationship of NAFLD with cardiovascular death were reported in 6 studies,[15,16,18,21-23] pooling a total population of 23,549 (NAFLD 30.27%) followed-up for a median of 24.1 years (IQR 5-12, 976,175 patient-years). Patients with NAFLD did not show increased risk of cardiovascular death when compared to controls (OR, 1.13; 95% CI, 0.57-2.23; $P = 0.656$). The random-effects model showed considerable heterogeneity, with an I^2 of 79%. Funnel plot asymmetry was not assessed by Egger's test due to low number of studies ($n < 10$) (Figure 1).

NAFLD and Cardiovascular Morbidity

Myocardial Infarction. Data on the relationship of NAFLD with myocardial infarction were reported in 4 studies,[13,23-25] pooling a total population of 9,856,437 (NAFLD 1.49%) followed-up for a median of 24.1 years (IQR 5-12, 49,900,021 patient-years). Patients with NAFLD showed increased risk of myocardial infarction when compared to

controls (OR, 1.62; 95% CI, 1.53-1.72; $P < 0.001$). The random-effects model showed moderate heterogeneity, with an I^2 of 35% (Figure 2).

Cerebrovascular Disease. Data on the relationship of NAFLD with stroke were reported in 9 studies,[13,18,23-29] pooling a total population of 9,867,187 (NAFLD 1.53%) followed-up for a median of 24.1 years (IQR 5-12, 50,006,973 patient-years). Patients with NAFLD had increased risk of cardiovascular events when compared to controls (OR, 1.60; 95% CI, 1.21-2.12; $P = 0.005$). The random-effects model showed substantial heterogeneity, with an I^2 of 58% (Figure 2).

Atrial Fibrillation. Data on the relationship of NAFLD with incident atrial fibrillation were reported in 4 studies,[30-33] pooling a total population of 337,698 (NAFLD 25.03%) followed-up for a median of 24.1 years (IQR 5-12, 1,816,019 patient-years). Patients with NAFLD had increased risk of atrial fibrillation when compared to controls (OR, 1.68; 95%CI 1.22-2.3; $p = 0.001$). The random-effects model showed substantial heterogeneity, with an I^2 of 60% (Figure 2).

MACCE. Data on the relationship of NAFLD with MACCE were reported in 11 studies,[14,15,18,19,24,25,27-29,34,35] pooling a total population of 91,977 (NAFLD 31.9%) followed-up for a median of 24.1 years (IQR 5-12, 963,307 patient-years). Patients with NAFLD had increased risk of cardiovascular events when compared to controls (OR, 2.32; 95% CI, 1.28-4.19; $P = 0.01$). The random-effects model showed considerable heterogeneity, with an I^2 of 89%. Funnel plot asymmetry was assessed by means of the Egger's test, which showed a *P*-value of 0.27, indicating nonsignificant asymmetry (Figure 2).

Subgroup Analysis. By categorizing studies based on geographic location, cohorts from Eastern countries showed lower CV mortality compared to Western countries (OR 0.54 [95% CI, 0.25-1.16] vs 1.46 [95% CI, 1.09-1.95], respectively; $P = 0.02$ for subgroup differences; Figure 1). The same trend was observed for all-cause mortality data, however, in this case the subgroup analysis did not achieve statistical significance (OR 0.77 and 1.42, respectively; $P = 0.05$ for subgroup differences). All other subgroup analyses based on geographic location did not result in significant differences between NAFLD and non-NAFLD cohorts.

Assessment of Study Quality, Small Study Effect, and Publication Bias. The overall quality of included studies was high (Fig S1), however, most

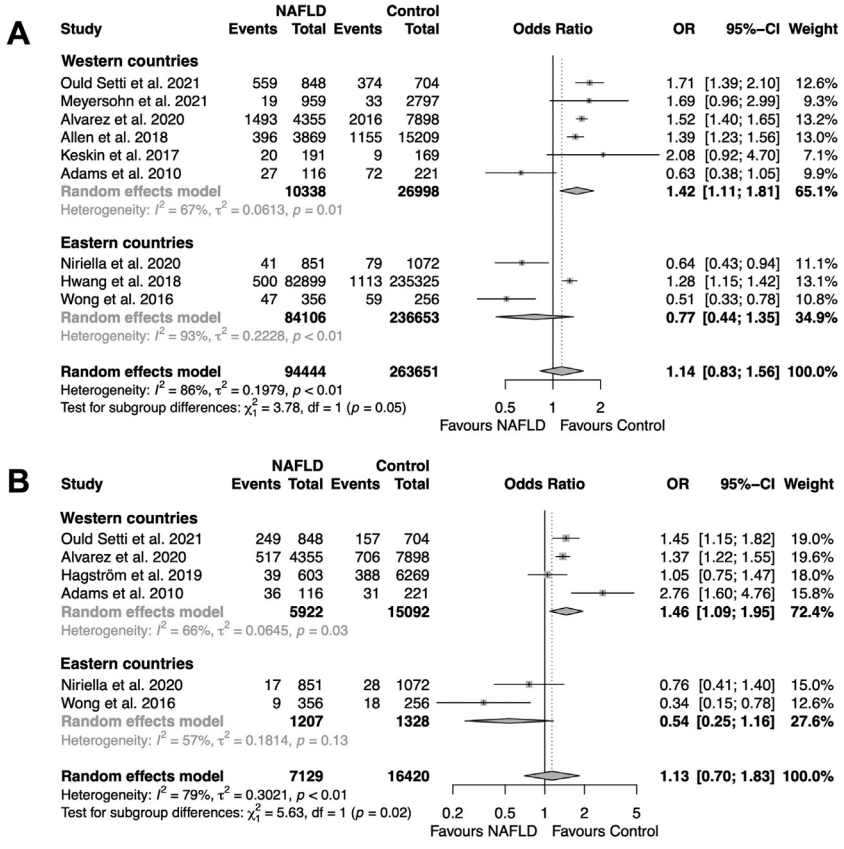

FIG 1. NAFLD and mortality. Forest plots for A) All-Cause Mortality and B) Cardiovascular Mortality.

studies likely suffered from attrition bias. Visual evaluation of constructed funnel plots with the trim-and-fill technique did not show evidence of small study effects or publication bias. Egger's test for funnel plot asymmetry was only performed on the MACCE sub-analysis due to low number of studies for other outcomes (n < 10 studies). In the MACCE sub-analysis, there was nonsignificant funnel plot asymmetry ($P = 0.27$).

Sensitivity Analysis and Evaluation of Sources of Heterogeneity. Leave-one-out sensitivity analysis was performed for all outcomes (Fig S4). No single study significantly affected computed effect size (Fig S3). A Baujat plot was also produced to elucidate contribution of a single study to the overall random-effect model heterogeneity. Studies by Niriella[15] and Wong[18] contributed by more than 15% to the overall model heterogeneity

in the CV death meta-analysis, but exerted a negligible effect on the pooled effect size (Fig S5).

Lean Versus Non-Lean NAFLD. Data regarding the prognostic significance of NAFLD in lean versus non-lean individuals were extracted from 10 studies published between 2017 and 2022, resulting in an overall pooled population of 13,629 NAFLD patients followed up for an average of 9.1 years (IQR 6.4-8.2, 100,415 patient-years). Among all included NAFLD cohorts, prevalence of lean patients was 20.19%. Categorization of BMI status varied across included studies: a detail of each study's definition of lean and non-lean status is provided in Table S1. For this specific analysis we leveraged both restrospective and prospective outcome data, only available for all-cause mortality, CV mortality, and MACCE Figure 3.

All-cause Mortality. Data on the relationship of lean NAFLD with all-cause death were reported in 8 studies,[36-43] pooling a total population of 12,652 (lean 20.57%) followed-up for a median of 9.1 years (IQR 6-8 years 93,638 patient-years). Lean patients with NAFLD showed a trend toward increased mortality when compared to non-lean, however, this finding did not reach statistical significance (OR 1.49; 95% CI, 0.93-2.37; $P = 0.08$). The random-effects model showed considerable heterogeneity, with an I^2 of 83%.

CV Mortality. Data on the relationship of lean NAFLD with cardiovascular death were reported in 4 studies,[23,36,37,41] pooling a total NAFLD population of 6928 (lean 27.17%) followed-up for a median of 9.1 years (IQR 6.4-8.2, 55,437 patient-years). Lean patients with NAFLD showed increased risk of cardiovascular death when compared to non-lean (OR 1.50; 95% CI, 1.12-2.00; $P = 0.006$). The random-effects model showed no heterogeneity, with an I^2 of 0%.

MACCE. Data on the relationship of lean NAFLD with MACCE were reported in 7 studies,[36-38,40,43-45] pooling a total NAFLD population of 8049 (lean 12.73%) followed-up for a median of 9.1 years (IQR6.4-8.2, 53,060 patient-years). Lean patients with NAFLD showed similar risk of cardiovascular events when compared to non-lean; the model did not reach statistical significance (OR, 0.93; 95% CI, 0.7-1.22; $P = 0.514$). The random-effects model showed low heterogeneity, with an I^2 of 29%.

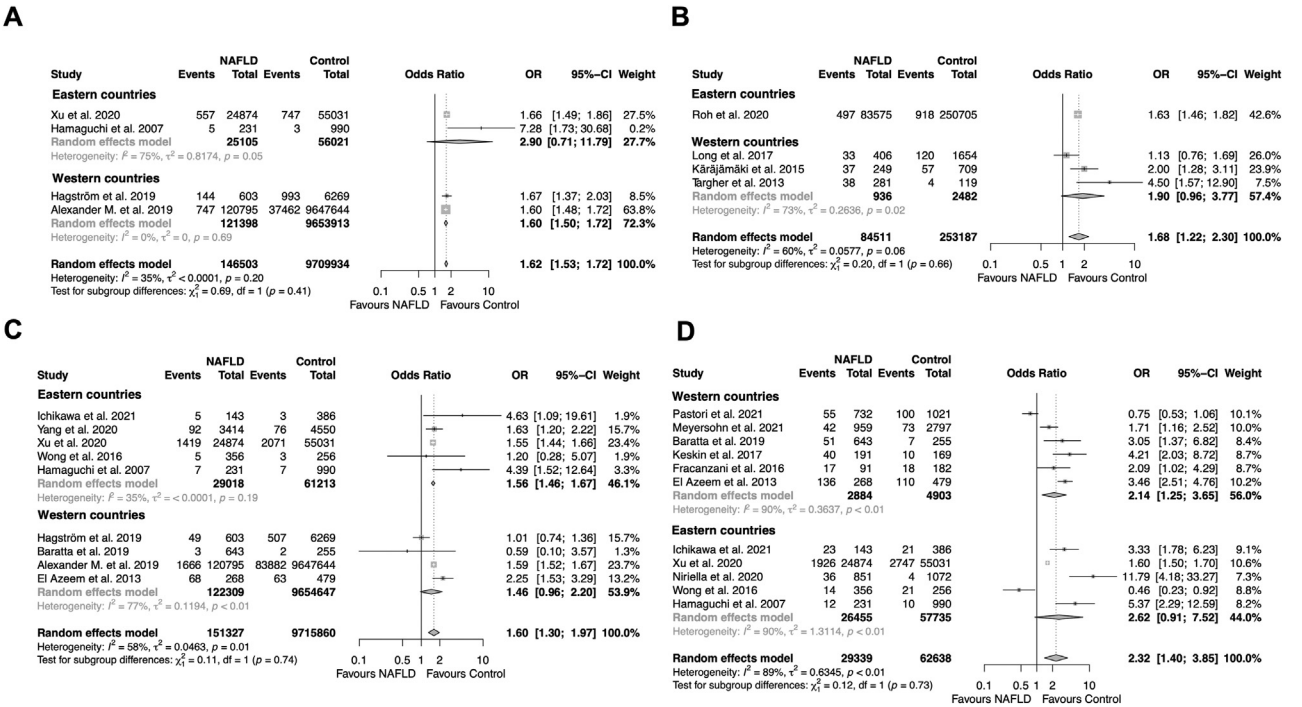

FIG 2. NAFLD and cardiovascular morbidity. Forest plots for A) myocardial infarction, B) ischaemic stroke, C) atrial fibrillation, and D) MACCE in NAFLD patients versus non-NAFLD controls.

Discussion

The main findings of the current meta-analysis provide evidence of the association between NAFLD and increased CV risk, particularly regarding myocardial infarction, stroke, atrial fibrillation, and major adverse cardiac and cerebrovascular events (*Central Illustration*). However, NAFLD was not associated with increased all-cause and CV mortality, in contrast to previous reports.[46] Interestingly, we found a distinct difference between Eastern and Western world regarding impact of NAFLD on CV mortality: risk estimates of CV death were significantly higher in pooled cohorts from Western countries. While the observed geographical gradient on CV death might be multifactorial and linked to underlying genetic susceptibility with exposure to different lifestyle and dietary habits[47]; the nonsignificant impact on all-cause mortality might be a consequence of similar rates of liver-related deaths and non-CV comorbidities. As for myocardial infarction and stroke, we found that NAFLD was associated with a 60% increased risk, in agreement with previous studies.[48,49] Also, based on our results, NAFLD was associated with increased risk of incident AF. It has been previously pointed out that NAFLD, as well as elevated transaminases, are independent risk factors for AF[50,51]; this effect may be due to the specific NAFLD metabolic milieu determining an alteration of atrial conduction properties.[52]

Influence of BMI differed between Eastern and Western countries; in particular, being overweight or obese was associated with greater all-cause mortality in Western countries, but not in Eastern countries. Risk of all-cause death and future CV disease was elevated in lean patients compared to non-lean. While a number of uneven confounders should be carefully considered, the «obesity paradox» should be taken also into account.[53] Further, while the lean NAFLD definition was homogeneous across most studies enrolling lean patients (BMI <25 kg/m^2), three studies identified Asian patients as lean based on BMI <23[41,44,45] as recommended by international guidelines in these ethnic groups.[54] Nevertheless, pooled effect sizes do clearly indicate significant health risk in the lean NAFLD population, with CV event rates at least comparable to their non-lean counterparts. Several studies have compared the clinical characteristics and outcomes of lean non-lean NAFLD. These studies have found that lean NAFLD is associated with a higher prevalence of metabolic abnormalities such as insulin resistance, dyslipidemia, and hypertension, compared to non-lean NAFLD. Additionally, lean NAFLD is associated with a higher risk of developing liver fibrosis and cirrhosis, as well as a higher risk of liver-related mortality.

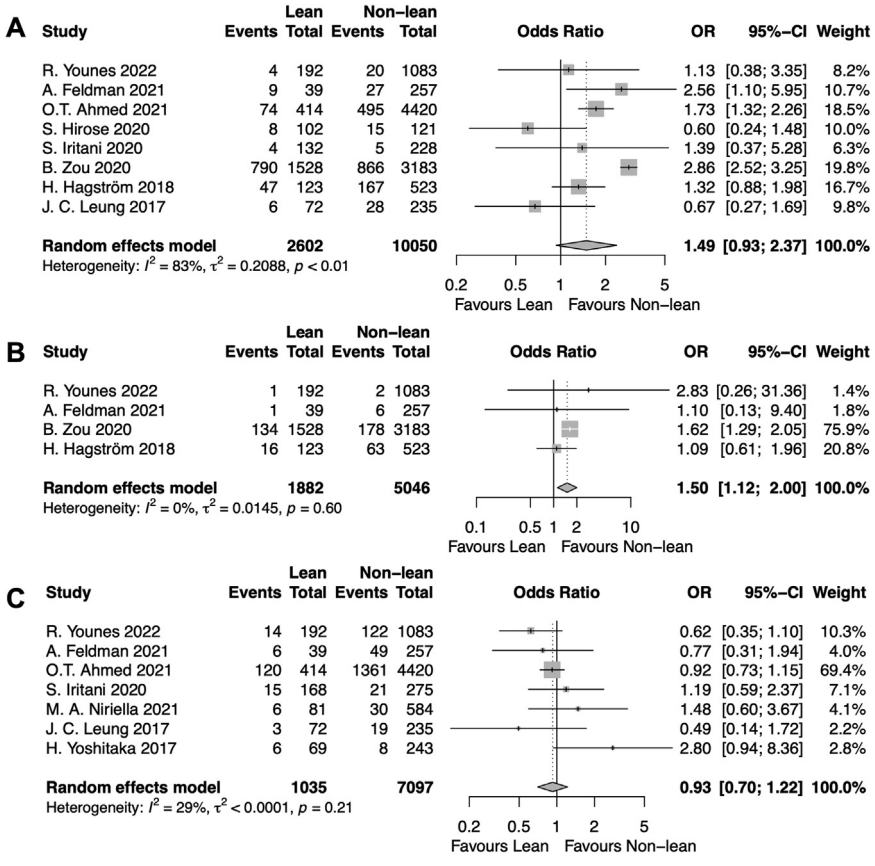

FIG 3. Lean versus non-lean NAFLD. Forest plots for A) All-Cause Mortality, B) Cardiovascular Mortality, and C) MACCE in patients with lean NAFLD versus non-lean NAFLD.

Current prediction models depict a worrisome NAFLD pandemic. Not only will the incidence of disease will grow, but more advanced forms of disease (ie steatohepatitis and advanced fibrosis) are expected to increase even faster.[55] In 2021, a NAFLD Preparedness Index was proposed by the NAFLD Policy Review Collaborators.[56] According to a global study of 102 countries, NAFLD is not receiving enough attention in national health agendas, with around a third of countries receiving a score of zero on the Preparedness Index, and no single country achieving a score of >50/100. The World Health Organization and other international organizations can play a crucial role in supporting national efforts to address NAFLD. In this context, the results of this systematic review and meta-analysis highlight the need for greater social and political awareness on NAFLD as a CV risk factor.

Strengths and Limitations

We acknowledge strengths and limitations of our analysis. To the best of our knowledge, this meta-analysis is an original contribution pooling results of studies comparing CV outcomes between lean and non-lean NAFLD phenotypes. Secondly, our comparison of NAFLD versus non-NAFLD individuals strictly relies on prospective cohorts. Further, we reported relevant differences in CV risk across Eastern and Western countries, particularly concerning rates of myocardial infarction, CV death, and all-cause death. A few limitations should be also addressed. Both main and subgroup analyses were affected by significant statistical heterogeneity. In the main analysis, it is likely that use of different diagnostic modalities to identify presence of NAFLD could partially account for the observed heterogeneity. Indeed, studies by Alexander et al.[13] and Allen et al.[20] enrolled NAFLD patients by ICD codes, and potentially retrieved on elevated transaminase levels. Moreover, it has been previously reported that both ultrasonography and computed tomography are suboptimal imaging modalities for biopsy-proven NAFLD,[57] yet ultrasonography is by far the most common diagnostic modality for NAFLD identification (Table 1). Explorative subgroup analysis by diagnostic modality did not show statistically significant subgroup differences (see Supplementary Material); however, thorough evaluation of diagnostic and prognostic yield of all diagnostic modalities utilized to assess NAFLD presence was beyond the scope of the current systematic review. We do not report NAFLD-related risk of incident heart failure in the current meta-analysis, as the literature search did not yield prospective studies comparing NAFLD patients with non-NAFLD individuals. The finding of an excess mortality associated with lean NAFLD must be carefully interpreted. Indeed, selection bias and failing to control for major confounder, such as metabolic syndrome, may introduce systematic distortion in the strength of association. Although the main meta-analysis was restricted to prospective studies, retrospective studies were accepted in the lean versus non-lean NAFLD subgroup analysis, due to scarcity of prospective outcome studies focusing on BMI. Another limitation of our work is that it does not tackle the most recent definition of metabolic dysfunction-associated liver disease, or MAFLD. Finally, while focusing on the overall clinical impact of hepatic steatosis, we did not assess the prognostic implications of severe NAFLD phenotypes, that is, steatohepatitis and hepatic fibrosis, also due to heterogeneity of definitions in the literature.

Conclusions

NAFLD portends higher risk of cardiovascular morbidity but does not predict increased all-cause and CV death. However, predicted mortality may vary across geographic locations, with higher CV mortality observed in Western countries. Patients with NAFLD are at high risk of CV consequences independent of their body mass status, and lean phenotypes should not be overlooked in risk assessment for CV disease prevention. Evaluation of NAFLD should be encouraged for CV screening purposes and should be the objective of further research to understand the underlying mechanisms linked to CV morbidity and to develop effective treatments.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interest

None.

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None

Supplementary materials

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